Doc Code: AP.PRE.REQ

| PRE-APPEAL BRIEF REQUEST FOR REVIEW | | Docket Number (Optional) WALLACH=27A |
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| I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 14550, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]<br>on _____<br>Signature _____<br>Typed or printed name _____ | Application Number 10/761,370 | Filed January 22, 2004 |
| | First Named Inventor David WALLACH | |
| | Art Unit 1633 | Examiner I. Popa |

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)

☒ attorney of record.
Registration number 25,618.

☐ attorney or agent acting under 37 CFR 1.34.

Registration number if acting under 37 CFR 1.34 _____

/rlb/
Signature

Roger L. Browdy
Typed or Printed Name

202-628-5197
Telephone number

October 29, 2008
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required.
Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

**REASONS WHY REVIEW IS REQUESTED**

In the advisory action of October 8, 2008, the examiner stated that applicant's proposed amendment of August 29, 2008, would be entered for the purpose of appeal and that the rejection of claims 20-23 under 35 U.S.C. 112, first paragraph , as introducing new matter had been overcome by the deletion of these claims. The only remaining rejection is the obviousness rejection of claims 1 and 17-19. However, this rejection is untenable and should be withdrawn without the necessity of filing an appeal brief.

Briefly, the present invention relates to antibodies specific for the novel RAP-2 protein. More specifically, claim1 is directed to a molecule comprising an antibody specific for a RAP-2 protein of the sequence SEQ ID NO:4, or a fragment of said antibody, which fragment is capable of binding to RAP-2. In claim 17, the antibody or fragment is a monoclonal antibody or fragment thereof. In claim 18, the antibody is a chimeric antibody and in claim 19, the molecule is detectably labeled.

The sole rejection of record in this case is a rejection of all of the claims as being unpatentable over Yongan (1996) [note the examiner erroneously indicated a date of 1966] in view of Yongan (1998) and Ellis. The examiner states that Yongan (1996) identifies the protein Fip-2, which can utilize interaction with induced cellular factors to activate apoptosis. The examiner recognizes that neither Yongan reference teaches anti-Fip-2 antibodies. However, the examiner states that it would have been obvious to raise antibodies directed to Fip-2 with a reasonable expectation of success. The motivation to do so would have been in order to study the interaction of Fip-2 with the cellular proteins involved in TNF-α induced apoptosis.

The examiner states that the present specification teaches that the leucine zipper domains and the C-terminus of RAP-2 encoded by SEQ ID NO:4 and Fip-2 are conserved. Thus, the examiner concludes that anti-Fip-2 antibodies recognizing these domains would necessarily be specific for RAP-2, thereby meeting the terms of claim 1. The examiner relies on Ellis as teaching that monoclonal and chimeric antibodies and detectable labels are known in the prior art and that one of ordinary skill in the art would have been motivated to use a monoclonal antibody in order to study

the function of specific domains in Fip-2 function or to use a humanized antibody that could be used in therapy for humans or to use a label in order to localize the protein inside the cell.

In response to applicant's arguments, the examiner stated that the fact that the overlapping regions between RAP-2 and Fip-2 are small and therefore a large percentage of monoclonal antibodies raised against Fip-2 would not bind to RAP-2 is irrelevant as the present claims encompass antibodies against the overlapping regions and the combined teaching of the prior art disclose such an antibody and therefore renders the invention *prima facie* obvious. In the advisory action, the examiner stated that the present claims do not recite that the antibody recognizes RAP-2 without recognizing Fip-2 and that the claims are drawn to a composition and not to a method of screening. The examiner states that the prior art cited teaches anti-Fip-2 antibodies and since Fip-2 and RAP-2 sequences overlap, such antibodies would necessarily comprise antibodies capable of recognizing RAP-2. This rejection is respectfully traversed.

It is essentially the examiner's position that if it is obvious to raise antibodies against a particular protein, then all possible antibodies that could be raised against that protein are unpatentable, regardless of any special and unexpected properties that such antibodies might have. But that is not the law. It is always possible to find specific antibodies within a genus of known antibodies, which specific antibodies have special properties that make them patentable despite the knowledge of the genus of antibodies that generally bind to the protein. The special, unexpected properties rebut any *prima facie* case of obviousness which arises from the genus.

In the present case, the examiner is stating that it would have been obvious to make antibodies against Fip-2. But the only known properties of such antibodies would be that they combine to Fip-2. The examiner sees fit to disregard the fact that a small portion of the total antibodies that can be raised against Fip-2 have a special and unexpected property that was totally unknown at the time of the present invention. That property is that such subset of Fip-2 antibodies can bind to RAP-2. This unexpected property of being able to bind not only to Fip-2, but also to RAP-2 rebuts any *prima facie* case of obviousness that the examiner has for the entire set of antibodies against Fip-2 most of which will not bind to RAP-2.

In the advisory action, the examiner states that the present claims do not recite that the antibody recognizes RAP-2 without recognizing Fip-2. Of course, this is correct, but all of the claims require that the antibodies bind to RAP-2. On the other hand, only a small subset of the total number of antibodies that would be raised against Fip-2 will also bind to RAP-2. In order to have in hand, from among the total antibodies against Fip-2, an antibody that will also bind to RAP-2, one must engage in selection from among the genus of antibodies suggested by the prior art. However, the prior art does not make obvious any type of selection from among the antibodies against Fip-2 so as to arrive at an antibody that will bind not only to Fip-2, but also to RAP-2.

The examiner states that the present claims are drawn to a composition and not to a method of screening, but this is beside the point. The fact is that the prior art only teaches an entire set of antibodies that binds to Fip-2. Only a small percentage of this set will also bind to RAP-2. In order to have such an antibody that will also bind to RAP-2, one must select from among the antibodies of Fip-2 and the prior art does not provide for such selection. The present claims require antibodies that bind to RAP-2. If one raised a thousand monoclonal antibodies that bind to Fip-2, why would it be obvious to select for only those antibodies that bind both Fip-2 and RAP-2? If the antibody binds Fip-2, but does not bind RAP-2, it does not fall within the scope of the present claims.

The fact that the set of antibodies raised against Fip-2 may comprise antibodies that bind to both Fip-2 and RAP-2 does not make that subset of antibodies that bind to both Fip-2 and RAP-2 obvious. This is not an anticipation rejection, it is an obviousness rejection and obviousness rejections can be overcome by showing of unexpected results. The present claims only encompass that subset of the total number antibodies that can possibly be raised against Fip-2 that bind to both Fip-2 and RAP-2, but the prior art does not direct one of ordinary skill in the art in any way to any antibodies within that subset. Furthermore, all of the antibodies within that subset possess unexpected properties. While all of the antibodies against Fip-2 would be expected to have the property of binding to Fip-2, it would have been totally unexpected at the time that the present invention was made that a small subset of those total antibodies would have the unexpected property

of binding to the novel RAP-2 protein. Accordingly, any *prima facie* case of obviousness established by the examiner has been overcome by this showing of unexpected results.

The present claims are not directed to monoclonal antibodies that bind both RAP-2 and Fip-2 nor are the present claims directed only to the antibodies against RAP-2 that do not bind to Fip-2. The present claims are directed to all antibodies that bind to RAP-2. Thus, the present claims exclude those antibodies of the prior art that bind Fip-2, but do not bind to RAP-2, i.e., the majority of the antibodies that could be raised against Fip-2.

With specific respect to claim 17, drawn to monoclonal antibodies or fragments of monoclonal antibodies, those of ordinary skill in the art would understand that in any given round of hybridoma production there is no guarantee that any of the monoclonal antibodies that are obtained by screening against Fip-2 would necessarily be directed to that portion of Fip-2 that happens to overlap with RAP-2. It is not inherent that any such antibodies would be raised. Certainly, those of ordinary skill in the art understand that it is common practice in the antibody art that antibodies that art not found in one round of hybridomas may be found in another and *vice-versa*. In any event, those of ordinary skill in the art would never know whether any given hybridoma found by the combination of references suggested by the examiner would fall within the scope of the present claims. This does not even establish a case of *prima facie* obviousness. The examiner has not discussed whether the regions of overlap are particularly immunogenic. One cannot simply assume that monoclonal antibodies can be raised against every possible region of a protein. Some regions may be folded within the protein or obscured. Thus, there is no certainty that a monoclonal antibody to the overlapping region could even be raised when looking generally for monoclonal antibodies that bind to Fip-2, let alone whether it would be obvious to select for that monoclonal antibody that happens to be directed to such an overlapping region. Accordingly, claim 17 should be considered in its own right.

Claim 18 should also be considered in its own right, as one cannot make a chimeric antibody until one has selected for a particular antibody that is desired to be made into a chimeric antibody. The present claims require that the antibody that is made into a chimeric antibody is one

that binds to RAP-2. The examiner has not provided any reason why one would particularly select for an antibody that binds to both Fip-2 and RAP-2 from among all of the antibodies allegedly made obvious by Yongan, so that such selected antibody could be subjected to the genetic engineering necessary to make a chimeric antibody. Accordingly, this claim is also patentable in its own right.

In conclusion, the examiner has only established an arguable *prima facie* case that it would be obvious to raise antibodies against Fip-2. The examiner has accepted the fact that only a small portion of those antibodies that could be obtained by using Fip-2 as an immunogen would be directed to the overlapping region so that they would also bind to RAP-2 as required by the present claims. The present claims are not directed to the full set of antibodies that could be raised against Fip-2. The present claims only encompass that part of the prior art genus of antibodies that binds to both Fip-2 and RAP-2. Those very specific antibodies, and particularly those specific monoclonal antibodies, that happen to bind to both Fip-2 and RAP-2 are not obvious because the prior art does not disclose any reason to select for them and the prior art does not recognize that such a subset has unexpected and important properties that are not possessed by all of the other antibodies that would be raised against Fip-2. Accordingly, any *prima facie* case of obviousness established by the examiner has been rebutted.

For all of these reasons, it is urged that this rejection be withdrawn following a pre-brief appeal conference and that this application be passed to allowance.